The Rejection of Claims 13 and 15-22 under 35 U.S.C. §112, second paragraph

Claims 13 and 15-22 stand rejected as indefinite. Applicant respectfully traverses.

The term "GPNMB" is objected to as having multiple meanings and being a mere laboratory term. However, GPNMB is actually a term of art. This is the designation which those of skill in the art have given to a particular gene. The specification at page 26, Table 2, last line, describes the gene with a gene name (Glycoprotein (transmembrane) *nmb*), a gene symbol (*GPNMB*), a cellular location (membrane), a GenBank number (X76534), primer pairs for amplification of the gene (SEQ ID NO: 15 and 16), and a literature citation (Weterman, 1995, *Int. J. Cancer 60:* 73-81).

If one uses the GenBank number one finds a particular amino acid sequence for the protein:

MECLYYFLGFLLLAARLPLDAAKRFHDVLGNERPSAYMREHNQLNGWSSDENDWNEK
LYPVWKRGDMRWKNSWKGGRVQAVLTSDSPALVGSNITFAVNLIFPRCQKEDANGNI
VYEKNCRNEAGLSADPYVYNWTAWSEDSDGENGTGQSHHNVFPDGKPFPHHPGWRR
WNFIYVFHTLGQYFQKLGRCSVRVSVNTANVTLGPQLMEVTVYRRHGRSTINYKWSFG
DNTGLFVSTNHTVNHTYVLNGTFSLNLTVKAAAPGPCPPPPPPPRPSKPTPSLGPAGDNP
LELSRIPDENCQINRYGHFQATITIVEGILEVNIIQMTDVLMPVPWPESSLIDFVVTCQGSIP
TEVCTIISDPTCEITQNTVCSPVDVDEMCLLTVRRTFNGSGTYCVNLTLGDDTSLALTSTL
ISVPDRDPASPLRMANSALISVGCLAIFVTVISLLVYKKHKEYNPIENSPGNVVRSKGLSV
FLNRAKAVFFPGNQEKDPLLKNQEFKGVS. See Tab A.

Thus the term GPNMB is neither indefinite nor a laboratory term. It has a specific meaning in the art which one of ordinary skill in the art would know, given the teachings of the specification. Although applicants do not believe it to be necessary, claim 13 has been amended to recite the longer name "Glycoprotein (transmembrane) *nmb*."

The term "contacting" in the phrase "contacting cells with an antibody" of claim 13 is said to be unclear. The Patent Office asks whether applicant intends "for the compounds to be delivered by placing the antibody in a cell of a glioblastoma."[1] The step of contacting does not require that an antibody be placed *in* a cell. It requires that the antibody be placed in contact

1 If the question arose due to the missing preposition in the claim as filed, that missing preposition ("with") has now been inserted by amendment.

with a cell. If the cell is in culture, then the antibody is placed in the culture medium. If the cell is in an animal, then the antibody is delivered into the animal so that the antibody can *contact* the cell.

The plain meaning of the word "contacting" is intended and there is no indefiniteness. The dictionary[2] defines the verb "to contact" as "to bring or put into contact." The noun "contact" is defined as "the coming together or touching of two objects or surfaces." These meanings are what applicant intends, as discussed with particularity above with regard to cells and antibodies.

The term "extracellular epitope" is also said to be indefinite because the metes and bounds cannot be defined. The Office Action explains that any combination of three or more amino acids found within the extracellular domain of GPNMB can be considered an epitope. Even if the definition of an extracellular epitope is accurately provided by the Office Action, it does not follow that the term is indefinite. The extracellular domain of GPNMB is a known domain of a known protein. The claim simply requires that the antibody which is used be capable of binding to the extracellular domain. The claim is clear and definite as written.

The Rejection of Claims 13 and 15-22 Under 35 U.S.C. §112, first paragraph

Claims 13 and 15-22 are rejected as not enabled by the specification. The specification allegedly does not enable any person skilled in the art to practice the invention commensurate in scope with these claims. This rejection is respectfully traversed.

The Office Action provides its rationales for the rejection at pages 4 and 5. They are quoted below and addressed individually.

- *"Nowhere in the specification does it specifically teach the delivery of an agent to a specific epitope of GPNMB, because the GPNMB protein has never actually been defined in the specification. There is little information of the protein itself."*

The Office Action urges that the protein is not defined. However, as pointed out above, the GPNMB protein was known in the art, and the specification references its complete amino

2 The American Heritage Dictionary, second college edition, Houghton Mifflin Company, Boston, 1982.

acid sequence in GenBank. It is not clear what additional information about the protein might be necessary to practice the invention.

Applicants have applied the SMART (Simple Modular Architecture Research Tool) tool to automatically identify the extracellular domain of GPNMB. SMART is made available to the public by the European Molecular Biology Laboratory on the Internet. As shown at Tab B, amino acids 1 to 483 have a >0.98 probability of being extracellular. Thus one or ordinary skill in the art would have no trouble identifying the extracellular domain or making antibodies which specifically bind to it.

- *"The specification does not teach whether the protein even actually exists."*

The specification implicitly teaches that the protein exists. The specification teaches throughout the use of antibodies specific for the protein. The specification teaches throughout the detection of elevated expression levels using Western blotting, enzyme-linked immunosorbent assay, radioimmunoassay, and fluorescence activated cell sorting. If the protein did not exist, then these teachings would be for nought.

Applicants may not, *arguendo,* have proven that the protein exists. However, applicants are not obliged to prove such things. The Patent Office is obliged to assume the truth of the specification's teachings unless it has good reason to doubt it. *See,* MPEP §2107.02, which quotes from *In re Marzocchi,* 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) as follows:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis added).

Thus, the specification's alleged failure to explicitly teach that the protein exists cannot render the specification not enabling.

- *"It is a well established fact that in normal circumstances, the level of transcription parallels that of translation, however, in certain circumstances, the level of mRNA transcription is uncoupled from protein translation. Therefore, given the fact that it is possible for some transcription and translation events to be unparalleled, it is possible GPNMB may not be translated from the unregulated mRNA detected in the instant invention."*(citations committed)

The Office Action speculates that GPNMB protein translation may be uncoupled from GPNMB mRNA transcription. This speculation is contrary to what the Office Action itself sets out as the "established fact in normal circumstances." There is no factual or evidentiary basis provided by the Office Action for asserting that GPNMB departs from the normal circumstance. However, as stated in the MPEP, there must be a "reason to doubt the objective truth of the statements contained therein." Mere speculation about a possibility is not a reason to doubt. Thus this rationale cannot properly serve as a basis for rejecting the claims as not enabled.

- *"How would one of skill in the art know whether there are even enough epitopes present on the surface of a glioblastoma for the method to be effective in delivering an agent."*

The Office Action speculates that one requires a certain number of epitopes to make delivery effective. However, the specification teaches that the GPNMB protein is highly expressed in glioblastoma. See, *e.g.*, Figure 3. Moreover, the amino acid sequence of GPNMB protein indicates that 483/560 residues are likely to be extracellular (*i.e.*, 86 % of the protein). See Tab B. Thus, the record evidence suggests that there will be sufficient extracellular epitopes on the surface of glioblastoma cells. The imputation to the contrary has no factual or scientific basis.

- *"If there is only a small percentage of protein found on the surface of the glioblastoma cell, then the antibody conjugate that is administered is left circulating in the blood stream thereby eliciting anti-idiotypic antibodies."*

The Office Action speculates that administration of an antibody-conjugate may cause a presumably undesirable side effect, elicitation of anti-idiotypic antibodies. The Office Action does not explain how that would render the claimed method unworkable. Nonetheless, this is again mere speculation, without the slightest bit of evidentiary support or scientific basis.

- *"Because the working examples of the instant invention have only provided a method of screening, amplification, hybridization, and other general methods of probing, it is not commensurate in scope to the claims that read on methods of delivering a reagent using an antibody to GPNMB."*

The Office Action makes the false equation that the scope of the ***working examples*** must be commensurate with the scope of the claims. In fact, the law requires that the scope of the ***specification's teachings as a whole*** must be commensurate with the scope of the claims ("the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims." MPEP §2164.08. The absence of working examples is not determinative of non-enablement. "How a teaching is set forth, by specific example or broad terminology, is not important." MPEP §2164.08.

The Patent Office has not met its burden in showing that the specification does not provide enablement that is commensurate with the scope of the claims. The burden is on the Patent Office to "back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement [of the application]." See MPEP § 2164.04. The Patent Office has simply used speculation without ever providing evidence inconsistent with the teachings of the specification. Withdrawal of this rejection is requested because the Patent Office has not made a *prima facie* case of non-enablement.

The Rejection of Claims 13, 15, 18-20 and 22 under 35 U.S.C. §102(b)

Claims 13, 15, 18-20, and 22 stand rejected as anticipated by Johnson (U.S. 5,352,447). This rejection is respectfully traversed.

Johnson is cited as teaching use of an antibody that specifically recognizes the transferrin receptor.

Claims 13, 15, 18-20 and 22 are directed to use of an antibody that specifically binds to an extracellular epitope of GPNMB.

GPNMB and transferrin receptor are two distinct proteins. The office action provides no evidence whatsoever that they are the same protein or even that they are similar proteins. In the absence of any such evidence, there is no reasonable basis on which to conclude that these proteins share epitopes. There is no reasonable basis to conclude that antibodies specific for transferrin receptor would specifically bind to GPNMB. The PTO has failed to meet its burden in presenting a *prima facie* case of anticipation, inherency, or equivalence.

Current estimates of the complexity of the human genome are in the range of 40,000 genes. The assumption of a one-to-one correspondence of genes-to-proteins would lead to an estimate of 40,000 proteins in the human proteome. There is no reason to believe that any two of 40,000 proteins selected at random would be similar in sequence.

The PTO justifies its conclusion of equivalence of the transferrin receptor and GPNMB on the basis of the failure of applicants to provide the sequence of GPNMB. However, as discussed above, the sequence of GPNMB is known in the art and is cited in the specification. No sequence for transferrin receptor is found in the cited Johnson patent. Nonetheless, applicants have compared the sequences of human transferrin receptor proteins 1 (Tab C) and 2 (Tab D) to the sequence of GPNMB (Tab A). The NCBI's Blast 2 Sequences tool was used. No significant similarity was found. See Tabs E and F.

The Rejection of Claims 13, 15, and 18-21 under 35 U.S.C. §103(a)

Claims 13, 15, and 18-21 stand rejected as unpatentable over Lazarus in view of either Reiter or Maynard. This rejection is respectfully traversed.

Lazarus, the primary reference, is cited as teaching the assessment of anti-NMB antibodies. The PTO asserts that NMB of Lazarus is also known as GPNMB. This, however, is a false assertion. Lazarus teaches that Neuromedin B is a decapeptide, *i.e.*, a ten-amino acid residue peptide. See page 161, column 1, first sentence. The sequence of neuromedin B is provided in Lazarus' Table 1, line 1: GNLWATGHFM-NH2. This sequence does not appear in

the sequence of GPNMB (NP_002501). Thus the basis for the rejection must collapse as NMB and GPNMB are not the same protein, as erroneously asserted by the PTO.

Lazarus' neuromedin B decapeptide is produced *in vivo* from a 121amino acid-residue protein. See NP_066563, particularly residues 47-56 (Tab G).

Applicants compared the NMB, NP_066563, 121 residue sequence to the 560 residue GPNMB sequence of NP_002501 (Tab H) using the Blast 2 Sequences program of the NCBI.[3] No significant similarity was found. (See Tab I.) Thus, the PTO's contention that NMB and GPNMB are the same is simply not true.

Applicants also searched the entire GenBank CDS translations using BlastP and the neuromedin B, 121-residue sequence. Of the 18 hits, none were GPNMB. See Tab J.

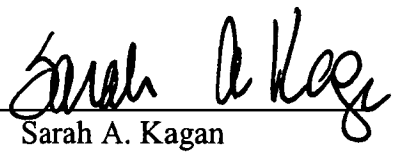
Reiter and Maynard do not remedy this deficiency. Both are cited as teaching "conjugation of antibodies in general to either toxic agents or labels for the treatment or imaging of cancer." Thus, even if one were motivated to combine the teachings of the cited reference, one would not achieve the present invention. None of the cited references teaches antibodies to GPNMB.

Withdrawal of this rejection is respectfully requested.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Dated: July 14, 2003

By: 
Sarah A. Kagan
Registration No. 32,141

Customer No. 22907

3 Note that the protein sequences are derived from the gene sequence M21551.1 and X76534:1. Each of these gene sequences is cited in the specification at Table 2.

Entrez Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Boo

Search Nucleotide for Go Clear

Limits Preview/Index History Clipboard Details

Display default Show: 1 Send to File Get Subsequence

1: X76534. H.sapiens NMB mRN...[gi:666042] Links

```
LOCUS       HSNMB                   2669 bp    mRNA    linear   PRI 09-FEB-1995
DEFINITION  H.sapiens NMB mRNA.
ACCESSION   X76534
VERSION     X76534.1  GI:666042
KEYWORDS    NMB gene.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 2669)
  AUTHORS   Weterman,M.A., Ajubi,N., van Dinter,I.M., Degen,W.G., van
            Muijen,G.N., Ruitter,D.J. and Bloemers,H.P.
  TITLE     nmb, a novel gene, is expressed in low-metastatic human melanoma
            cell lines and xenografts
  JOURNAL   Int. J. Cancer 60 (1), 73-81 (1995)
  MEDLINE   95113576
   PUBMED   7814155
REFERENCE   2
  AUTHORS   Weterman,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (03-DEC-1993) M. Weterman, University of Nijmegen, Dept
            of Biochemistry, PO Box 9101, 6500 HB Nijmegen, NETHERLANDS
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                     PFPHHPGWRRWNFIYVFHTLGQYFQKLGRCSVRVSVNTANVTLGPQLMEVTVYRRHGR
                     AYVPIAQVKDVYVVTDQIPVFVTMFQKNDRNSSDETFLKDLPIMFDVLIHDPSHFLNY
                     STINYKWSFGDNTGLFVSTNHTVNHTYVLNGTFSLNLTVKAAAPGPCPPPPPPPRPSK
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                     PESSLIDFVVTCQGSIPTEVCTIISDPTCEITQNTVCSPVDVDEMCLLTVRRTFNGSG
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BASE COUNT      752 a    595 c    597 g    725 t
ORIGIN
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      481 atatgtttac aactggacag catggtcaga ggacagtgac ggggaaaatg gcaccggcca
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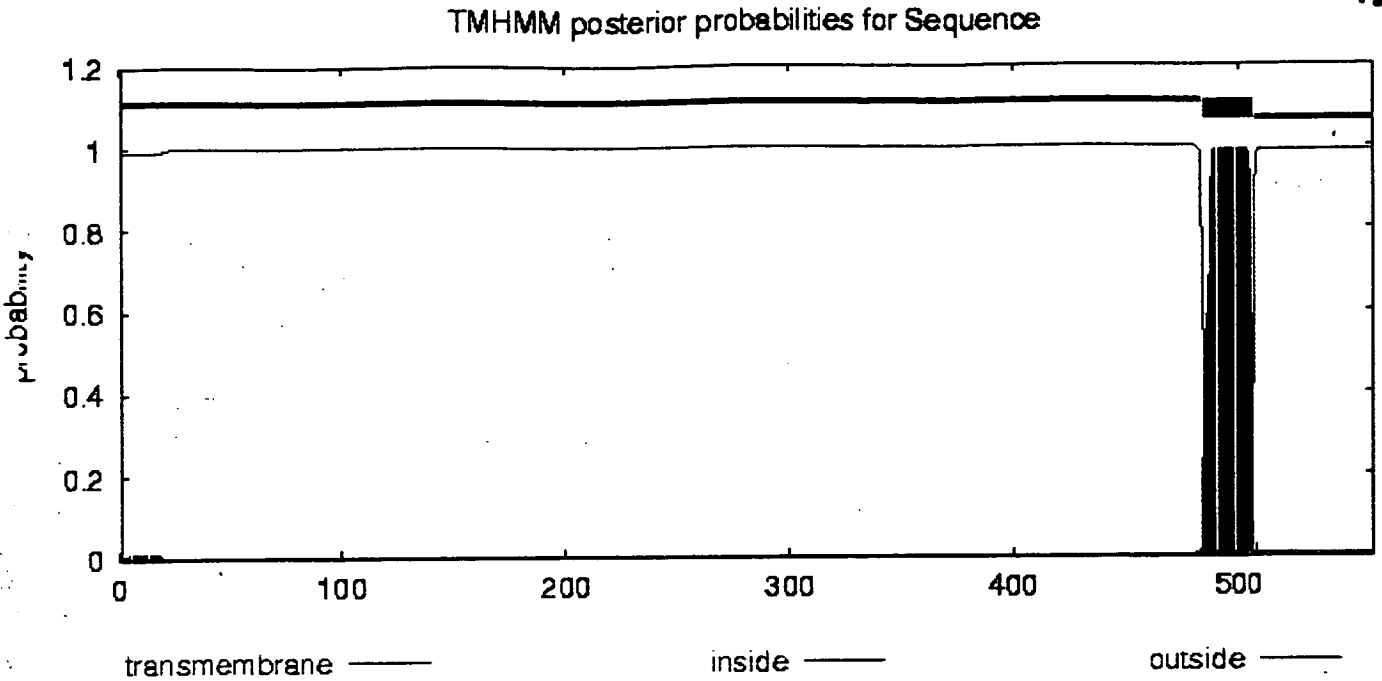
Tab B



Tab B

Sarah Kagan

From: Ben Aghdasi
Sent: Friday, April 25, 2003 2:48 PM
To: Sarah Kagan
Subject: I have also left a copy of the following results on you desk.

TMHMM
result.gif

Sarah,
This program predicts extracellular and intercellular of the protein.
The figure is in color and listed below is probability table used to draw the figure above.

As seen from 1-483 amino acid has a probability of >0.98 to be Extracellular and from 509-560 amino acid has a probability of >0.98 to be intercellular

Probability table.
Sequence

#	AA	inside	membr	outside
1	M	0.01149	0.00000	0.98851
2	E	0.00781	0.00368	0.98851
3	C	0.00452	0.00697	0.98851
4	L	0.00452	0.00708	0.9884
5	Y	0.00107	0.01057	0.98837
6	Y	0.00107	0.01057	0.98837
7	F	0.00092	0.01071	0.98837
8	L	0.00092	0.01071	0.98837
9	G	0.00092	0.01071	0.98837
10	F	0.00092	0.01071	0.98837
11	L	0.00092	0.01071	0.98837
12	L	0.00092	0.01071	0.98837
13	L	0.00092	0.01071	0.98837
14	A	0.00092	0.01071	0.98837
15	A	0.00092	0.01071	0.98837
16	R	0.00092	0.01071	0.98837
17	L	0.00092	0.01068	0.98841
18	P	0.00092	0.01040	0.98868
19	L	0.00093	0.01019	0.98888
20	D	0.00102	0.00527	0.99371
21	A	0.00103	0.00344	0.99553
22	A	0.00104	0.00299	0.99596
23	K	0.00105	0.00017	0.99878
24	R	0.00105	0.00011	0.99884
25	F	0.00105	0.00007	0.99888
26	H	0.00106	0.00005	0.9989
27	D	0.00106	0.00003	0.99892
28	V	0.00106	0.00002	0.99892
29	L	0.00106	0.00002	0.99893
30	G	0.00106	0.00000	0.99895
31	N	0.00106	0.00000	0.99895
32	E	0.00106	0.00000	0.99895
33	R	0.00106	0.00000	0.99895
34	P	0.00106	0.00000	0.99895
35	S	0.00106	0.00000	0.99895
36	A	0.00106	0.00000	0.99895
37	Y	0.00106	0.00000	0.99895
38	M	0.00106	0.00000	0.99895
39	R	0.00106	0.00000	0.99895
40	E	0.00106	0.00000	0.99895
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42	N	0.00106	0.00000	0.99895

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48	S	0.00106	0.00000	0.99895
49	S	0.00106	0.00000	0.99895
50	D	0.00106	0.00000	0.99895
51	E	0.00106	0.00000	0.99895
52	N	0.00106	0.00000	0.99895
53	D	0.00106	0.00000	0.99895
54	W	0.00106	0.00000	0.99895
55	N	0.00106	0.00000	0.99895
56	E	0.00106	0.00000	0.99895
57	K	0.00106	0.00000	0.99895
58	L	0.00106	0.00000	0.99895
59	Y	0.00106	0.00000	0.99895
60	P	0.00106	0.00000	0.99895
61	V	0.00106	0.00000	0.99895
62	W	0.00106	0.00000	0.99895
63	K	0.00106	0.00000	0.99895
64	R	0.00106	0.00000	0.99895
65	G	0.00106	0.00000	0.99895
66	D	0.00106	0.00000	0.99895
67	M	0.00106	0.00000	0.99895
68	R	0.00106	0.00000	0.99895
69	W	0.00106	0.00000	0.99895
70	K	0.00106	0.00000	0.99895
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74	K	0.00105	0.00000	0.99895
75	G	0.00104	0.00002	0.99894
76	G	0.00103	0.00003	0.99894
77	R	0.00102	0.00004	0.99893
78	V	0.00099	0.00008	0.99893
79	Q	0.00099	0.00010	0.99892
80	A	0.00090	0.00026	0.99884
81	V	0.00088	0.00032	0.9988
82	L	0.00088	0.00032	0.99879
83	T	0.00088	0.00033	0.99879
84	S	0.00088	0.00034	0.99879
85	D	0.00088	0.00034	0.99878
86	S	0.00088	0.00036	0.99877
87	P	0.00087	0.00036	0.99876
88	A	0.00087	0.00037	0.99876
89	L	0.00087	0.00037	0.99876
90	V	0.00087	0.00037	0.99876
91	G	0.00087	0.00037	0.99876
92	S	0.00087	0.00037	0.99876
93	N	0.00087	0.00037	0.99876
94	I	0.00087	0.00037	0.99876
95	T	0.00087	0.00037	0.99876
96	F	0.00087	0.00036	0.99876
97	A	0.00087	0.00036	0.99877
98	V	0.00088	0.00034	0.99878
99	N	0.00088	0.00031	0.99881
100	L	0.00088	0.00031	0.99881
101	I	0.00089	0.00028	0.99883
102	F	0.00091	0.00025	0.99884
103	P	0.00100	0.00008	0.99892
104	R	0.00105	0.00001	0.99894
105	C	0.00105	0.00001	0.99894
106	Q	0.00105	0.00000	0.99894
107	K	0.00106	0.00000	0.99894
108	E	0.00106	0.00000	0.99894
109	D	0.00106	0.00000	0.99894
110	A	0.00106	0.00000	0.99894
111	N	0.00106	0.00000	0.99894
112	G	0.00106	0.00000	0.99894
113	N	0.00106	0.00000	0.99894

114	I	0.00106	0.00000	0.99894
115	V	0.00106	0.00000	0.99894
116	Y	0.00106	0.00000	0.99894
117	E	0.00106	0.00000	0.99894
118	K	0.00106	0.00000	0.99894
119	N	0.00106	0.00000	0.99894
120	C	0.00106	0.00000	0.99894
121	R	0.00106	0.00000	0.99894
122	N	0.00106	0.00000	0.99894
123	E	0.00106	0.00000	0.99894
124	A	0.00106	0.00000	0.99894
125	G	0.00106	0.00000	0.99894
126	L	0.00106	0.00000	0.99894
127	S	0.00106	0.00000	0.99894
128	A	0.00106	0.00000	0.99894
129	D	0.00106	0.00000	0.99894
130	P	0.00106	0.00000	0.99894
131	Y	0.00106	0.00000	0.99894
132	V	0.00106	0.00000	0.99894
133	Y	0.00106	0.00000	0.99894
134	N	0.00106	0.00000	0.99894
135	W	0.00106	0.00000	0.99894
136	T	0.00106	0.00000	0.99894
137	A	0.00106	0.00000	0.99894
138	W	0.00106	0.00000	0.99894
139	S	0.00106	0.00000	0.99894
140	E	0.00106	0.00000	0.99894
141	D	0.00106	0.00000	0.99894
142	S	0.00106	0.00000	0.99894
143	D	0.00106	0.00000	0.99894
144	G	0.00106	0.00000	0.99894
145	E	0.00106	0.00000	0.99894
146	N	0.00106	0.00000	0.99894
147	G	0.00106	0.00000	0.99894
148	T	0.00106	0.00000	0.99894
149	G	0.00106	0.00000	0.99894
150	Q	0.00106	0.00000	0.99894
151	S	0.00106	0.00000	0.99894
152	H	0.00106	0.00000	0.99894
153	H	0.00106	0.00000	0.99894
154	N	0.00106	0.00000	0.99894
155	V	0.00106	0.00000	0.99894
156	F	0.00106	0.00000	0.99894
157	P	0.00106	0.00000	0.99894
158	D	0.00106	0.00000	0.99894
159	G	0.00106	0.00000	0.99894
160	K	0.00106	0.00000	0.99894
161	P	0.00106	0.00000	0.99894
162	F	0.00106	0.00000	0.99894
163	P	0.00106	0.00000	0.99894
164	H	0.00106	0.00000	0.99894
165	H	0.00106	0.00000	0.99894
166	P	0.00105	0.00000	0.99894
167	G	0.00105	0.00001	0.99894
168	W	0.00105	0.00001	0.99894
169	R	0.00105	0.00001	0.99894
170	R	0.00105	0.00001	0.99893
171	W	0.00105	0.00002	0.99893
172	N	0.00105	0.00002	0.99893
173	F	0.00105	0.00002	0.99893
174	I	0.00105	0.00002	0.99893
175	Y	0.00105	0.00002	0.99893
176	V	0.00105	0.00002	0.99893
177	F	0.00105	0.00002	0.99893
178	H	0.00105	0.00002	0.99893
179	T	0.00105	0.00002	0.99893
180	L	0.00105	0.00002	0.99893
181	G	0.00105	0.00002	0.99893
182	Q	0.00105	0.00002	0.99893
183	Y	0.00105	0.00002	0.99893
184	F	0.00105	0.00002	0.99893

185	Q	0.00106	0.00001	0.99893
186	K	0.00106	0.00001	0.99893
187	L	0.00106	0.00001	0.99893
188	G	0.00106	0.00000	0.99893
189	R	0.00106	0.00000	0.99893
190	C	0.00106	0.00000	0.99893
191	S	0.00106	0.00001	0.99893
192	V	0.00106	0.00001	0.99893
193	R	0.00106	0.00001	0.99893
194	V	0.00106	0.00001	0.99893
195	S	0.00106	0.00001	0.99893
196	V	0.00106	0.00001	0.99893
197	N	0.00106	0.00001	0.99893
198	T	0.00106	0.00001	0.99893
199	A	0.00106	0.00001	0.99893
200	N	0.00106	0.00001	0.99893
201	V	0.00106	0.00001	0.99893
202	T	0.00106	0.00001	0.99893
203	L	0.00106	0.00001	0.99893
204	G	0.00106	0.00001	0.99893
205	P	0.00106	0.00001	0.99893
206	Q	0.00106	0.00001	0.99893
207	L	0.00106	0.00001	0.99893
208	M	0.00106	0.00001	0.99893
209	E	0.00106	0.00001	0.99893
210	V	0.00106	0.00001	0.99893
211	T	0.00106	0.00001	0.99893
212	V	0.00106	0.00001	0.99893
213	Y	0.00106	0.00001	0.99893
214	R	0.00106	0.00000	0.99894
215	R	0.00106	0.00000	0.99894
216	H	0.00106	0.00000	0.99894
217	G	0.00106	0.00000	0.99894
218	R	0.00106	0.00000	0.99894
219	A	0.00106	0.00000	0.99894
220	Y	0.00106	0.00000	0.99894
221	V	0.00106	0.00001	0.99893
222	P	0.00106	0.00001	0.99893
223	I	0.00106	0.00001	0.99893
224	A	0.00106	0.00001	0.99893
225	Q	0.00106	0.00001	0.99893
226	V	0.00106	0.00001	0.99893
227	K	0.00106	0.00001	0.99893
228	D	0.00106	0.00001	0.99893
229	V	0.00106	0.00001	0.99893
230	Y	0.00106	0.00001	0.99893
231	V	0.00106	0.00001	0.99893
232	V	0.00106	0.00001	0.99893
233	T	0.00106	0.00001	0.99893
234	D	0.00106	0.00001	0.99893
235	Q	0.00106	0.00001	0.99893
236	I	0.00106	0.00001	0.99893
237	P	0.00106	0.00001	0.99893
238	V	0.00106	0.00001	0.99893
239	F	0.00106	0.00001	0.99893
240	V	0.00106	0.00001	0.99893
241	T	0.00106	0.00001	0.99893
242	M	0.00106	0.00000	0.99893
243	F	0.00106	0.00000	0.99893
244	Q	0.00106	0.00000	0.99894
245	K	0.00106	0.00000	0.99894
246	N	0.00106	0.00000	0.99894
247	D	0.00106	0.00000	0.99894
248	R	0.00106	0.00000	0.99894
249	N	0.00106	0.00000	0.99894
250	S	0.00106	0.00000	0.99894
251	S	0.00106	0.00000	0.99894
252	D	0.00106	0.00000	0.99894
253	E	0.00106	0.00000	0.99894
254	T	0.00106	0.00000	0.99894
255	F	0.00106	0.00000	0.99894

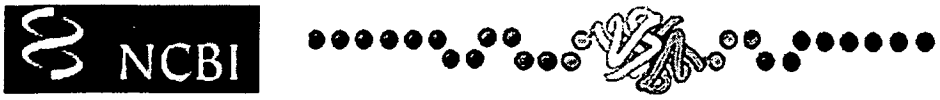
256	L	0.00106	0.00000	0.99894
257	K	0.00106	0.00000	0.99894
258	D	0.00106	0.00000	0.99894
259	L	0.00106	0.00000	0.99893
260	P	0.00106	0.00000	0.99893
261	I	0.00106	0.00000	0.99893
262	M	0.00106	0.00000	0.99893
263	F	0.00106	0.00000	0.99893
264	D	0.00106	0.00000	0.99893
265	V	0.00106	0.00000	0.99893
266	L	0.00106	0.00000	0.99893
267	I	0.00106	0.00000	0.99893
268	H	0.00106	0.00000	0.99893
269	D	0.00106	0.00000	0.99893
270	P	0.00106	0.00000	0.99893
271	S	0.00106	0.00000	0.99893
272	H	0.00106	0.00000	0.99893
273	F	0.00106	0.00000	0.99893
274	L	0.00106	0.00000	0.99893
275	N	0.00106	0.00000	0.99893
276	Y	0.00106	0.00000	0.99893
277	S	0.00106	0.00000	0.99893
278	T	0.00106	0.00000	0.99893
279	I	0.00106	0.00000	0.99893
280	N	0.00107	0.00000	0.99893
281	Y	0.00107	0.00000	0.99893
282	K	0.00107	0.00000	0.99893
283	W	0.00107	0.00000	0.99893
284	S	0.00107	0.00000	0.99893
285	F	0.00107	0.00001	0.99893
286	G	0.00107	0.00000	0.99893
287	D	0.00107	0.00000	0.99893
288	N	0.00107	0.00001	0.99893
289	T	0.00107	0.00001	0.99893
290	G	0.00107	0.00001	0.99892
291	L	0.00107	0.00001	0.99892
292	F	0.00107	0.00001	0.99892
293	V	0.00107	0.00001	0.99892
294	S	0.00107	0.00001	0.99892
295	T	0.00107	0.00001	0.99892
296	N	0.00107	0.00001	0.99892
297	H	0.00107	0.00001	0.99892
298	T	0.00107	0.00001	0.99892
299	V	0.00107	0.00001	0.99892
300	N	0.00107	0.00001	0.99892
301	H	0.00107	0.00001	0.99892
302	T	0.00107	0.00001	0.99892
303	Y	0.00107	0.00001	0.99892
304	V	0.00106	0.00001	0.99892
305	L	0.00107	0.00001	0.99892
306	N	0.00107	0.00001	0.99892
307	G	0.00107	0.00001	0.99892
308	T	0.00107	0.00001	0.99892
309	F	0.00107	0.00001	0.99892
310	S	0.00107	0.00001	0.99892
311	L	0.00107	0.00001	0.99892
312	N	0.00107	0.00001	0.99892
313	L	0.00107	0.00001	0.99892
314	T	0.00107	0.00000	0.99892
315	V	0.00107	0.00000	0.99892
316	K	0.00108	0.00000	0.99892
317	A	0.00108	0.00000	0.99892
318	A	0.00108	0.00000	0.99892
319	A	0.00108	0.00000	0.99892
320	P	0.00108	0.00000	0.99892
321	G	0.00108	0.00000	0.99892
322	P	0.00108	0.00000	0.99892
323	C	0.00108	0.00000	0.99892
324	P	0.00108	0.00000	0.99892
325	P	0.00108	0.00000	0.99892
326	P	0.00108	0.00000	0.99892

327	P	0.00108	0.00000	0.99892
328	P	0.00108	0.00000	0.99892
329	P	0.00108	0.00000	0.99892
330	P	0.00108	0.00000	0.99892
331	R	0.00108	0.00000	0.99892
332	P	0.00108	0.00000	0.99892
333	S	0.00108	0.00000	0.99892
334	K	0.00108	0.00000	0.99892
335	P	0.00108	0.00000	0.99892
336	T	0.00108	0.00000	0.99892
337	P	0.00108	0.00000	0.99892
338	S	0.00108	0.00000	0.99892
339	L	0.00108	0.00000	0.99892
340	G	0.00108	0.00000	0.99892
341	P	0.00108	0.00000	0.99892
342	A	0.00108	0.00000	0.99892
343	G	0.00108	0.00000	0.99892
344	D	0.00108	0.00000	0.99892
345	N	0.00108	0.00000	0.99892
346	P	0.00108	0.00000	0.99892
347	L	0.00108	0.00000	0.99892
348	E	0.00108	0.00000	0.99892
349	L	0.00108	0.00000	0.99892
350	S	0.00108	0.00000	0.99892
351	R	0.00108	0.00000	0.99892
352	I	0.00108	0.00000	0.99892
353	P	0.00108	0.00000	0.99892
354	D	0.00108	0.00000	0.99892
355	E	0.00108	0.00000	0.99892
356	N	0.00108	0.00000	0.99892
357	C	0.00108	0.00000	0.99892
358	Q	0.00108	0.00000	0.99892
359	I	0.00107	0.00001	0.99891
360	N	0.00107	0.00002	0.99891
361	R	0.00106	0.00003	0.99891
362	Y	0.00104	0.00013	0.99883
363	G	0.00104	0.00015	0.99881
364	H	0.00103	0.00017	0.99879
365	F	0.00103	0.00018	0.99879
366	Q	0.00102	0.00018	0.99879
367	A	0.00102	0.00019	0.99879
368	T	0.00102	0.00020	0.99879
369	I	0.00101	0.00020	0.99878
370	T	0.00101	0.00021	0.99878
371	I	0.00100	0.00021	0.99878
372	V	0.00100	0.00021	0.99878
373	E	0.00100	0.00021	0.99878
374	G	0.00100	0.00021	0.99878
375	I	0.00100	0.00021	0.99878
376	L	0.00100	0.00021	0.99878
377	E	0.00100	0.00021	0.99878
378	V	0.00100	0.00021	0.99878
379	N	0.00101	0.00021	0.99878
380	I	0.00101	0.00020	0.99878
381	I	0.00104	0.00018	0.99878
382	Q	0.00113	0.00007	0.99881
383	M	0.00113	0.00006	0.99881
384	T	0.00113	0.00005	0.99882
385	D	0.00114	0.00003	0.99884
386	V	0.00114	0.00003	0.99884
387	L	0.00114	0.00003	0.99884
388	M	0.00114	0.00002	0.99884
389	P	0.00114	0.00002	0.99885
390	V	0.00114	0.00002	0.99885
391	P	0.00114	0.00001	0.99885
392	W	0.00114	0.00001	0.99886
393	P	0.00114	0.00000	0.99886
394	E	0.00114	0.00000	0.99886
395	S	0.00114	0.00000	0.99885
396	S	0.00114	0.00001	0.99885
397	L	0.00114	0.00001	0.99885

398	I	0.00114	0.00001	0.99885
399	D	0.00114	0.00001	0.99885
400	F	0.00114	0.00001	0.99885
401	V	0.00114	0.00001	0.99885
402	V	0.00114	0.00001	0.99885
403	T	0.00114	0.00001	0.99885
404	C	0.00114	0.00001	0.99885
405	Q	0.00114	0.00001	0.99885
406	G	0.00114	0.00001	0.99885
407	S	0.00114	0.00001	0.99885
408	I	0.00114	0.00001	0.99885
409	P	0.00114	0.00001	0.99885
410	T	0.00114	0.00001	0.99885
411	E	0.00114	0.00001	0.99885
412	V	0.00114	0.00001	0.99885
413	C	0.00114	0.00001	0.99885
414	T	0.00114	0.00001	0.99885
415	I	0.00114	0.00001	0.99885
416	I	0.00114	0.00001	0.99885
417	S	0.00115	0.00000	0.99885
418	D	0.00115	0.00000	0.99885
419	P	0.00115	0.00000	0.99885
420	T	0.00115	0.00000	0.99885
421	C	0.00115	0.00000	0.99885
422	E	0.00115	0.00000	0.99885
423	I	0.00115	0.00000	0.99885
424	T	0.00115	0.00000	0.99885
425	Q	0.00115	0.00000	0.99885
426	N	0.00115	0.00000	0.99885
427	T	0.00115	0.00000	0.99885
428	V	0.00115	0.00000	0.99885
429	C	0.00115	0.00000	0.99885
430	S	0.00115	0.00000	0.99885
431	P	0.00115	0.00000	0.99885
432	V	0.00115	0.00000	0.99885
433	D	0.00115	0.00000	0.99885
434	V	0.00115	0.00000	0.99885
435	D	0.00115	0.00000	0.99885
436	E	0.00115	0.00000	0.99885
437	M	0.00115	0.00000	0.99885
438	C	0.00115	0.00000	0.99885
439	L	0.00115	0.00000	0.99885
440	L	0.00115	0.00000	0.99885
441	T	0.00115	0.00000	0.99885
442	V	0.00115	0.00000	0.99885
443	R	0.00115	0.00000	0.99885
444	R	0.00115	0.00000	0.99885
445	T	0.00114	0.00001	0.99884
446	F	0.00113	0.00002	0.99884
447	N	0.00113	0.00003	0.99884
448	G	0.00112	0.00005	0.99884
449	S	0.00111	0.00006	0.99883
450	G	0.00109	0.00011	0.99881
451	T	0.00092	0.00030	0.99877
452	Y	0.00074	0.00050	0.99876
453	C	0.00072	0.00053	0.99876
454	V	0.00070	0.00055	0.99875
455	N	0.00070	0.00055	0.99875
456	L	0.00070	0.00056	0.99874
457	T	0.00070	0.00056	0.99874
458	L	0.00070	0.00056	0.99874
459	G	0.00070	0.00056	0.99874
460	D	0.00070	0.00056	0.99874
461	D	0.00070	0.00056	0.99874
462	T	0.00070	0.00056	0.99874
463	S	0.00070	0.00056	0.99874
464	L	0.00070	0.00056	0.99874
465	A	0.00070	0.00055	0.99875
466	L	0.00070	0.00055	0.99875
467	T	0.00071	0.00055	0.99875
468	S	0.00071	0.00054	0.99875

469	T	0.00071	0.00053	0.99876
470	L	0.00071	0.00052	0.99877
471	I	0.00071	0.00050	0.99879
472	S	0.00072	0.00047	0.99882
473	V	0.00075	0.00041	0.99884
474	P	0.00080	0.00017	0.99903
475	D	0.00081	0.00001	0.99919
476	R	0.00081	0.00000	0.99919
477	D	0.00081	0.00000	0.99919
478	P	0.00081	0.00001	0.99918
479	A	0.00081	0.00024	0.99895
480	S	0.00081	0.00065	0.99853
481	P	0.00081	0.00126	0.99793
482	L	0.00081	0.00527	0.99391
483	R	0.00080	0.01342	0.98577
484	M	0.00072	0.23647	0.76281
485	A	0.00030	0.54536	0.45434
486	N	0.00025	0.58448	0.41528
487	S	0.00018	0.68094	0.31887
488	A	0.00007	0.91632	0.08361
489	L	0.00001	0.98533	0.01466
490	I	0.00000	0.99200	0.008
491	S	0.00000	0.99227	0.00772
492	V	0.00000	0.99245	0.00755
493	G	0.00000	0.99247	0.00753
494	C	0.00000	0.99247	0.00753
495	L	0.00000	0.99247	0.00753
496	A	0.00000	0.99247	0.00753
497	I	0.00000	0.99247	0.00753
498	F	0.00000	0.99247	0.00753
499	V	0.00000	0.99247	0.00753
500	T	0.00003	0.99244	0.00753
501	V	0.00004	0.99243	0.00753
502	I	0.00048	0.99199	0.00753
503	S	0.00161	0.99085	0.00753
504	L	0.00325	0.98921	0.00754
505	L	0.01311	0.97933	0.00756
506	V	0.05549	0.93691	0.0076
507	Y	0.41061	0.58161	0.00778
508	K	0.96651	0.02517	0.00832
509	K	0.98966	0.00200	0.00834
510	H	0.99112	0.00054	0.00834
511	K	0.99165	0.00001	0.00834
512	E	0.99166	0.00000	0.00834
513	Y	0.99166	0.00000	0.00834
514	N	0.99166	0.00000	0.00834
515	P	0.99166	0.00000	0.00834
516	I	0.99166	0.00000	0.00834
517	E	0.99166	0.00000	0.00834
518	N	0.99166	0.00000	0.00834
519	S	0.99165	0.00001	0.00834
520	P	0.99165	0.00001	0.00834
521	G	0.99164	0.00002	0.00834
522	N	0.99164	0.00002	0.00834
523	V	0.99163	0.00003	0.00834
524	V	0.99163	0.00003	0.00834
525	R	0.99163	0.00003	0.00834
526	S	0.99162	0.00004	0.00834
527	K	0.99161	0.00005	0.00834
528	G	0.99155	0.00011	0.00834
529	L	0.99155	0.00011	0.00834
530	S	0.99155	0.00011	0.00834
531	V	0.99155	0.00011	0.00834
532	F	0.99155	0.00011	0.00834
533	L	0.99155	0.00011	0.00834
534	N	0.99155	0.00011	0.00834
535	R	0.99155	0.00011	0.00834
536	A	0.99155	0.00011	0.00834
537	K	0.99155	0.00011	0.00834
538	A	0.99155	0.00011	0.00834
539	V	0.99155	0.00011	0.00834

540	F	0.99155	0.00011	0.00834
541	F	0.99155	0.00011	0.00835
542	P	0.99155	0.00010	0.00835
543	G	0.99155	0.00008	0.00838
544	N	0.99155	0.00005	0.0084
545	Q	0.99155	0.00004	0.00841
546	E	0.99155	0.00001	0.00844
547	K	0.99155	0.00000	0.00845
548	D	0.99155	0.00000	0.00845
549	P	0.99155	0.00000	0.00845
550	L	0.99155	0.00000	0.00845
551	L	0.99155	0.00000	0.00845
552	K	0.99155	0.00000	0.00845
553	N	0.99155	0.00000	0.00845
554	Q	0.99155	0.00000	0.00845
555	E	0.99155	0.00000	0.00845
556	F	0.99155	0.00000	0.00845
557	K	0.99155	0.00000	0.00845
558	G	0.99155	0.00000	0.00845
559	V	0.99155	0.00000	0.00845
560	S	0.99155	0.00000	0.00845



☐ **1:** P02786. Transferrin recep...[gi:136378] BLink, Domains, Links

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LOCUS       P02786                  760 aa            linear   PRI 15-SEP-2003
DEFINITION  Transferrin receptor protein 1 (TfR1) (TR) (TfR) (Trfr) (CD71
            antigen) (T9) (p90).
ACCESSION   P02786
VERSION     P02786  GI:136378
DBSOURCE    swissprot: locus TFR1_HUMAN, accession P02786;
            class: standard.
            extra accessions:Q9UCN0,Q9UCU5,Q9UDF9,Q9UK21,created: Jul 21, 1986.
            sequence updated: Jul 21, 1986.
            annotation updated: Sep 15, 2003.
            xrefs: gi: 37432, gi: 37433, gi: 339515, gi: 339516, gi: 6164847,
            gi: 6164848, gi: 12654696, gi: 12654697, gi: 72139, pdb accession
            1CX8, pdb accession 1DE4
            xrefs (non-sequence databases): MEROPSM28.972, GlycoSuiteDBP02786,
            GenewHGNC:11763, MIM 190010, GOGO:0005768, GOGO:0005576,
            GOGO:0005887, GOGO:0004998, GOGO:0006879, InterProIPR003137,
            PfamPF02225, PfamPF04389, PfamPF04253
KEYWORDS    Transmembrane; Glycoprotein; Receptor; Lipoprotein; Palmitate;
            Signal-anchor; Endocytosis; Phosphorylation; Polymorphism;
            3D-structure.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 760)
  AUTHORS   Schneider,C., Owen,M.J., Banville,D. and Williams,J.G.
  TITLE     Primary structure of human transferrin receptor deduced from the
            mRNA sequence
  JOURNAL   Nature 311 (5987), 675-678 (1984)
  MEDLINE   85012743
  REMARK    SEQUENCE FROM N.A.
REFERENCE   2  (residues 1 to 760)
  AUTHORS   McClelland,A., Kuhn,L.C. and Ruddle,F.H.
  TITLE     The human transferrin receptor gene: genomic organization, and the
            complete primary structure of the receptor deduced from a cDNA
            sequence
  JOURNAL   Cell 39 (2 Pt 1), 267-274 (1984)
  MEDLINE   85048936
  REMARK    SEQUENCE FROM N.A.
REFERENCE   3  (residues 1 to 760)
  AUTHORS   Evans,P. and Kemp,J.
  TITLE     Exon/intron structure of the human transferrin receptor gene
  JOURNAL   Gene 199 (1-2), 123-131 (1997)
  MEDLINE   98019079
  REMARK    SEQUENCE FROM N.A.
            TISSUE=Placenta
REFERENCE   4  (residues 1 to 760)
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AUTHORS Wheeler,D.L.
TITLE Molecular and evolutionary studies of the transferrin receptor
JOURNAL Thesis (1999)
REMARK SEQUENCE FROM N.A.
TISSUE=Placenta

REFERENCE 5 (residues 1 to 760)
AUTHORS Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G., Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D., Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K., Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F., Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L., Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L., Scheetz,T.E., Brownstein,M.J., Usdin,T.B., Toshiyuki,S., Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J., Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J., McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S., Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W., Villalon,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A., Fahey,J., Helton,E., Ketteman,M., Madan,A., Rodrigues,S., Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y., Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D., Dickson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M., Butterfield,Y.S.N., Krzywinski,M.I., Skalska,U., Smailus,D.E., Schnerch,A., Schein,J.E., Jones,S.J.M. and Marra,M.A.
TITLE Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
MEDLINE 22388257
REMARK SEQUENCE FROM N.A.
TISSUE=Eye

REFERENCE 6 (residues 1 to 760)
AUTHORS Shih,Y.J., Baynes,R.D., Hudson,B.G., Flowers,C.H., Skikne,B.S. and Cook,J.D.
TITLE Serum transferrin receptor is a truncated form of tissue receptor
JOURNAL J. Biol. Chem. 265 (31), 19077-19081 (1990)
MEDLINE 91035436
REMARK SEQUENCE OF 101-119 (STFR).

REFERENCE 7 (residues 1 to 760)
AUTHORS Baynes,R.D., Shih,Y.J., Hudson,B.G. and Cook,J.D.
TITLE Characterization of transferrin receptor released by K562 erythroleukemia cells
JOURNAL Proc Soc Exp Biol Med 197 (4), 416-423 (1991)
MEDLINE 91334496
REMARK SEQUENCE OF 101-123 (STFR), AND CHARACTERIZATION.
TISSUE=Erythroleukemia

REFERENCE 8 (residues 1 to 760)
AUTHORS Coppolino,M., Migliorini,M., Argraves,W.S. and Dedhar,S.
TITLE Identification of a novel form of the alpha 3 integrin subunit: covalent association with transferrin receptor
JOURNAL Biochem. J. 306 (Pt 1), 129-134 (1995)
MEDLINE 95169043
REMARK SEQUENCE OF 288-302; 694-708 AND 721-730.
TISSUE=Prostatic carcinoma

REFERENCE 9 (residues 1 to 760)
AUTHORS Chicz,R.M., Urban,R.G., Lane,W.S., Gorga,J.C., Stern,L.J., Vignali,D.A. and Strominger,J.L.
TITLE Predominant naturally processed peptides bound to HLA-DR1 are derived from MHC-related molecules and are heterogeneous in size
JOURNAL Nature 358 (6389), 764-768 (1992)
MEDLINE 92375195

REMARK SEQUENCE OF 680-696.
REFERENCE 10 (residues 1 to 760)
AUTHORS Jing,S.Q. and Trowbridge,I.S.
TITLE Identification of the intermolecular disulfide bonds of the human transferrin receptor and its lipid-attachment site
JOURNAL EMBO J. 6 (2), 327-331 (1987)
MEDLINE 87218484
REMARK PALMITOYLATION OF CYS-62.
REFERENCE 11 (residues 1 to 760)
AUTHORS Alvarez,E., Girones,N. and Davis,R.J.
TITLE Intermolecular disulfide bonds are not required for the expression of the dimeric state and functional activity of the transferrin receptor
JOURNAL EMBO J. 8 (8), 2231-2240 (1989)
MEDLINE 90005427
REMARK MUTAGENESIS OF CYSTEINES INVOLVED IN INTERMOLECULAR BONDS.
REFERENCE 12 (residues 1 to 760)
AUTHORS Jing,S.Q., Spencer,T., Miller,K., Hopkins,C. and Trowbridge,I.S.
TITLE Role of the human transferrin receptor cytoplasmic domain in endocytosis: localization of a specific signal sequence for internalization
JOURNAL J. Cell Biol. 110 (2), 283-294 (1990)
MEDLINE 90130619
REMARK INTERNALIZATION SEQUENCE, AND MUTAGENESIS OF TYR-20.
REFERENCE 13 (residues 1 to 760)
AUTHORS Do,S.I. and Cummings,R.D.
TITLE Presence of O-linked oligosaccharide on a threonine residue in the human transferrin receptor
JOURNAL Glycobiology 2 (4), 345-353 (1992)
MEDLINE 93043836
REMARK CARBOHYDRATE-LINKAGE SITES THR-104.
REFERENCE 14 (residues 1 to 760)
AUTHORS Hayes,G.R., Enns,C.A. and Lucas,J.J.
TITLE Identification of the O-linked glycosylation site of the human transferrin receptor
JOURNAL Glycobiology 2 (4), 355-359 (1992)
MEDLINE 93043837
REMARK CARBOHYDRATE-LINKAGE SITES THR-104.
REFERENCE 15 (residues 1 to 760)
AUTHORS Hayes,G.R., Williams,A., Costello,C.E., Enns,C.A. and Lucas,J.J.
TITLE The critical glycosylation site of human transferrin receptor contains a high-mannose oligosaccharide
JOURNAL Glycobiology 5 (2), 227-232 (1995)
MEDLINE 95299226
REMARK STRUCTURE OF CARBOHYDRATES ON ASN-727.
REFERENCE 16 (residues 1 to 760)
AUTHORS Buchegger,F., Trowbridge,I.S., Liu,L.F., White,S. and Collawn,J.F.
TITLE Functional analysis of human/chicken transferrin receptor chimeras indicates that the carboxy-terminal region is important for ligand binding
JOURNAL Eur. J. Biochem. 235 (1-2), 9-17 (1996)
MEDLINE 96202913
REMARK IDENTIFICATION OF LIGAND BINDING DOMAIN.
REFERENCE 17 (residues 1 to 760)
AUTHORS Collawn,J.F., Lai,A., Domingo,D., Fitch,M., Hatton,S. and Trowbridge,I.S.
TITLE YTRF is the conserved internalization signal of the transferrin receptor, and a second YTRF signal at position 31-34 enhances endocytosis
JOURNAL J. Biol. Chem. 268 (29), 21686-21692 (1993)

MEDLINE 94012749
REMARK MUTAGENESIS OF ENDOCYTOSIS SITE.
REFERENCE 18 (residues 1 to 760)
AUTHORS Alvarez,E., Girones,N. and Davis,R.J.
TITLE A point mutation in the cytoplasmic domain of the transferrin receptor inhibits endocytosis
JOURNAL Biochem. J. 267 (1), 31-35 (1990)
MEDLINE 90226333
REMARK MUTAGENESIS OF TYR-20.
REFERENCE 19 (residues 1 to 760)
AUTHORS Dubljevic,V., Sali,A. and Goding,J.W.
TITLE A conserved RGD (Arg-Gly-Asp) motif in the transferrin receptor is required for binding to transferrin
JOURNAL Biochem. J. 341 (Pt 1), 11-14 (1999)
MEDLINE 99306849
REMARK MUTAGENESIS OF RGD MOTIF.
REFERENCE 20 (residues 1 to 760)
AUTHORS West,A.P. Jr., Giannetti,A.M., Herr,A.B., Bennett,M.J., Nangiana,J.S., Pierce,J.R., Weiner,L.P., Snow,P.M. and Bjorkman,P.J.
TITLE Mutational analysis of the transferrin receptor reveals overlapping HFE and transferrin binding sites
JOURNAL J. Mol. Biol. 313 (2), 385-397 (2001)
MEDLINE 21659940
REMARK MUTAGENESIS.
REFERENCE 21 (residues 1 to 760)
AUTHORS Fuchs,H., Lucken,U., Tauber,R., Engel,A. and Gessner,R.
TITLE Structural model of phospholipid-reconstituted human transferrin receptor derived by electron microscopy
JOURNAL Structure 6 (10), 1235-1243 (1998)
MEDLINE 98455506
REMARK ELECTRON MICROSCOPY.
REFERENCE 22 (residues 1 to 760)
AUTHORS Lawrence,C.M., Ray,S., Babyonyshev,M., Galluser,R., Borhani,D.W. and Harrison,S.C.
TITLE Crystal structure of the ectodomain of human transferrin receptor
JOURNAL Science 286 (5440), 779-782 (1999)
MEDLINE 20002984
REMARK X-RAY CRYSTALLOGRAPHY (3.2 ANGSTROMS) OF 121-760.
REFERENCE 23 (residues 1 to 760)
AUTHORS Douabin-Gicquel,V., Soriano,N., Ferran,H., Wojcik,F., Palierne,E., Tamim,S., Jovelin,T., McKie,A.T., Le Gall,J.-Y., David,V. and Mosser,J.
TITLE Identification of 96 single nucleotide polymorphisms in eight genes involved in iron metabolism: efficiency of bioinformatic extraction compared with a systematic sequencing approach
JOURNAL Hum. Genet. 109 (4), 393-401 (2001)
MEDLINE 21558434
REMARK VARIANT GLY-142.
COMMENT ----------

[FUNCTION] Cellular uptake of iron occurs via receptor-mediated endocytosis of ligand-occupied transferrin receptor into specialized endosomes. Endosomal acidification leads to iron release. The apotransferrin-receptor complex is then recycled to

the cell surface with a return to neutral pH and the concomitant loss of affinity of apotransferrin for its receptor. Transferrin receptor is necessary for development of erythrocytes and the nervous system (By similarity). A second ligand, the heditary hemochromatosis protein HFE, competes for binding with transferrin for an overlapping C-terminal binding site.
[SUBUNIT] Homodimer; disulfide-linked. Binds one transferrin or HFE molecule per polypeptide chain. Binds the HLA class II histocompatibility antigen, DR1.
[SUBCELLULAR LOCATION] Type II membrane protein. The sTfr isoform is secreted.
[INDUCTION] Regulated by cellular iron levels through binding of the iron regulatory proteins, IRP1 and IRP2, to iron-responsive elements in the 3'-UTR. Up-regulated upon mitogenic stimulation.
[PTM] N- and O-glycosylated, phosphorylated and palmitoylated. The serum form is only glycosylated.
[PTM] Proteolytically cleaved on Arg-100 to produce the soluble serum form (sTfR).
[MISCELLANEOUS] Serum transferrin receptor (sTfR) is used as a means of detecting erythropoietin (EPO) misuse by athletes and as a diagnostic test for anemias resulting from a number of conditions including rheumatoid arthritis, pregnancy, irritable bowel syndrome and in HIV patients.
[MISCELLANEOUS] Canine and feline parvoviruses bind human and feline transferrin receptors and use these receptors to enter and infect cells.
[SIMILARITY] BELONGS TO PEPTIDASE FAMILY M28B.
[DATABASE] NAME=PROW; NOTE=CD guide CD71 entry;
WWW='http://www.ncbi.nlm.nih.gov/prow/cd/cd71.htm'.

FEATURES	Location/Qualifiers
source	1..760 /organism="Homo sapiens" /db_xref="taxon:9606"
gene	1..760 /gene="TFRC"
Protein	1..760 /gene="TFRC" /product="Transferrin receptor protein 1"
Region	1..67 /gene="TFRC" /region_name="Domain" /note="CYTOPLASMIC (POTENTIAL)."
Site	9..12 /gene="TFRC" /site_type="mutagenized" /note="FSNL->YTRF: ONLY 80 % AS ACTIVE AS WILD-TYPE RECEPTOR. UPTAKE OF THE RECEPTOR."
Site	20..34 /gene="TFRC" /site_type="mutagenized" /note="YTRFSLARQVDGDNS->PPGYSLARQVDYTRF: NO INFLUENCE ON ENDOCYTIC UPTAKE OF THE RECEPTOR."
Site	20..23 /gene="TFRC" /site_type="mutagenized" /note="YTRF->PPGY: ONLY 16% AS ACTIVE AS WILD-TYPE RECEPTOR."
Site	20..23 /gene="TFRC" /site_type="unclassified"

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                /note="ENDOCYTOSIS SIGNAL."
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                /site_type="mutagenized"
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                /site_type="mutagenized"
                /note="Y->G: ONLY 20% AS ACTIVE AS WILD-TYPE RECEPTOR."
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                /site_type="mutagenized"
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                /site_type="mutagenized"
                /note="T->TAA: ONLY 19% AS ACTIVE AS WILD-TYPE RECEPTOR."
     Site       21
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                /note="T->F: ONLY 88% AS ACTIVE AS WILD-TYPE RECEPTOR."
     Site       23
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                /site_type="mutagenized"
                /note="F->Y: ONLY 48% AS ACTIVE AS WILD-TYPE RECEPTOR."
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     Site       31..34
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                /site_type="mutagenized"
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                OF THE RECEPTOR."
     Site       47..50
                /gene="TFRC"
                /site_type="mutagenized"
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                UPTAKE OF THE RECEPTOR."
     Site       58..61
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     Site       62
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     Region     68..88
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                /note="SIGNAL-ANCHOR (TYPE-II MEMBRANE PROTEIN)
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                /note="EXTRACELLULAR (POTENTIAL)."
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                /note="R -> V (IN REF. 7; AA SEQUENCE)."
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     Region     142
                /gene="TFRC"
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                /note="LIGAND-BINDING."
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                /gene="TFRC"
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                TRANSFERRIN NOR HFE."
     Site       623
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                /site_type="mutagenized"
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                     /gene="TFRC"
                     /site_type="mutagenized"
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                     REDUCED AFFINITY FOR HFE."
     Site            641
                     /gene="TFRC"
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     Site            643
                     /gene="TFRC"
                     /site_type="mutagenized"
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                     BINDING TO HFE."
     Site            644
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                     /site_type="mutagenized"
                     /note="S->A: NO SIGNIFICANT EFFECT ON BINDING TO
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     Site            646..648
                     /gene="TFRC"
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                     TRANSFERRIN)."
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                     /site_type="mutagenized"
                     /note="R->A,H: NO BINDING TO TRANSFERRIN."
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                     /gene="TFRC"
                     /site_type="mutagenized"
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     Site            647
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                     /site_type="mutagenized"
                     /note="G->A: LARGE EFFECT ON AFFINITY FOR TRANSFERRIN.
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     Site            648
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                     /site_type="mutagenized"
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                     /gene="TFRC"
                     /site_type="mutagenized"
                     /note="D->A: 16% BINDING TO TRANSFERRIN."
     Site            650
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                     /site_type="mutagenized"
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                     /gene="TFRC"
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                     /note="N-LINKED (GLCNAC...). /FTId=CAR_000173."
ORIGIN
        1 mmdqarsafs nlfggeplsy trfslarqvd gdnshvemkl avdeeenadn ntkanvtkpk
```

```
       61 rcsgsicygt iavivfflig fmigylgyck gvepktecer lagtespvre epgedfpaar
      121 rlywddlkrk lsekldstdf tstikllnen syvpreagsq kdenlalyve nqfrefklsk
      181 vwrdqhfvki qvkdsaqnsv iivdkngrlv ylvenpggyv ayskaatvtg klvhanfgtk
      241 kdfedlytpv ngsivivrag kitfaekvan aeslnaigvl iymdqtkfpi vnaelsffgh
      301 ahlgtgdpyt pgfpsfnhtq fppsrssglp nipvqtisra aaeklfgnme gdcpsdwktd
      361 stcrmvtses knvkltvsnv lkeikilnif gvikgfvepd hyvvvgaqrd awgpgaaksg
      421 vgtalllkla qmfsdmvlkd gfqpsrsiif aswsagdfgs vgatewlegy lsslhlkaft
      481 yinldkavlg tsnfkvsasp llytliektm qnvkhpvtgq flyqdsnwas kvekltldna
      541 afpflaysgi pavsfcfced tdypylgttm dtykelieri pelnkvaraa aevagqfvik
      601 lthdvelnld yerynsqlls fvrdlnqyra dikemglslq wlysargdff ratsrlttdf
      661 gnaektdrfv mkklndrvmr veyhflspyv spkespfrhv fwgsgshtlp allenlklrk
      721 qnngafnetl frnqlalatw tiqgaanals gdvwdidnef
//
```

1: Q9UP52. Transferrin recep...[gi:20140912] BLink, Domains, Links

```
LOCUS       Q9UP52                   801 aa            linear   PRI 15-SEP-2003
DEFINITION  Transferrin receptor protein 2 (TfR2).
ACCESSION   Q9UP52
VERSION     Q9UP52  GI:20140912
DBSOURCE    swissprot: locus TFR2_HUMAN, accession Q9UP52;
            class: standard.
            extra accessions:O75422,Q9HA99,Q9NX67,created: Feb 28, 2003.
            sequence updated: Feb 28, 2003.
            annotation updated: Sep 15, 2003.
            xrefs: gi: 5596369, gi: 5596370, gi: 3135305, gi: 3135312, gi:
            10433313, gi: 10433314, gi: 7020497, gi: 7020498
            xrefs (non-sequence databases): HSSPP02786, MEROPSM28.973,
            GenewHGNC:11762, MIM 604720, MIM 604250, GOGO:0005887,
            GOGO:0004998, GOGO:0006826, InterProIPR003137, PfamPF02225,
            PfamPF04389, PfamPF04253
KEYWORDS    Transmembrane; Glycoprotein; Receptor; Signal-anchor; Alternative
            splicing; Disease mutation.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 801)
  AUTHORS   Kawabata,H., Yang,R., Hirama,T., Vuong,P.T., Kawano,S.,
            Gombart,A.F. and Koeffler,H.P.
  TITLE     Molecular cloning of transferrin receptor 2. A new member of the
            transferrin receptor-like family
  JOURNAL   J. Biol. Chem. 274 (30), 20826-20832 (1999)
  MEDLINE   99340005
   PUBMED   10409623
  REMARK    SEQUENCE FROM N.A. (ISOFORMS ALPHA AND BETA).
            TISSUE=Erythroleukemia, and Myeloid leukemia cells
REFERENCE   2  (residues 1 to 801)
  AUTHORS   Glockner,G., Scherer,S., Schattevoy,R., Boright,A., Weber,J.,
            Tsui,L.C. and Rosenthal,A.
  TITLE     Large-scale sequencing of two regions in human chromosome 7q22:
            analysis of 650 kb of genomic sequence around the EPO and CUTL1
            loci reveals 17 genes
  JOURNAL   Genome Res. 8 (10), 1060-1073 (1998)
  MEDLINE   99018118
   PUBMED   9799793
  REMARK    SEQUENCE FROM N.A. (ISOFORM GAMMA).
REFERENCE   3  (residues 1 to 801)
  AUTHORS   Isogai,T., Ota,T., Hayashi,K., Sugiyama,T., Otsuki,T., Suzuki,Y.,
            Nishikawa,T., Nagai,K., Sugano,S., Shiratori,A., Sudo,H.,
            Wagatsuma,M., Hosoiri,T., Kaku,Y., Kodaira,H., Kondo,H.,
            Sugawara,M., Takahashi,M., Chiba,Y., Ishida,S., Murakawa,K.,
            Ono,Y., Takiguchi,S., Watanabe,S., Kimura,K., Murakami,K.,
```

Ishii,S., Kawai,Y., Saito,K., Yamamoto,J., Wakamatsu,A., Nakamura,Y., Nagahari,K., Masuho,Y., Ninomiya,K. and Iwayanagi,T.
TITLE Direct Submission
JOURNAL Submitted (~AUG-2000)
REMARK SEQUENCE OF 1-158 AND 370-801 FROM N.A.
TISSUE=Carcinoma, and Embryo
REFERENCE 4 (residues 1 to 801)
AUTHORS Camaschella,C., Roetto,A., Cali,A., De Gobbi,M., Garozzo,G., Carella,M., Majorano,N., Totaro,A. and Gasparini,P.
TITLE The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22
JOURNAL Nat. Genet. 25 (1), 14-15 (2000)
MEDLINE 20264357
PUBMED 10802645
REMARK DISEASE.
REFERENCE 5 (residues 1 to 801)
AUTHORS Roetto,A., Totaro,A., Piperno,A., Piga,A., Longo,F., Garozzo,G., Cali,A., De Gobbi,M., Gasparini,P. and Camaschella,C.
TITLE New mutations inactivating transferrin receptor 2 in hemochromatosis type 3
JOURNAL Blood 97 (9), 2555-2560 (2001)
MEDLINE 21213521
PUBMED 11313241
REMARK VARIANT HFE3 LYS-172.
COMMENT ----------

[FUNCTION] Mediates cellular uptake of transferrin-bound iron in a non-iron dependent manner. May be involved in iron metabolism, hepatocyte function and erythrocyte differentiation.
[SUBUNIT] Homodimer.
[SUBCELLULAR LOCATION] Type II membrane protein. The beta isoform lacks the transmembrane domain and is probably intracellular.
[ALTERNATIVE PRODUCTS] Event=Alternative splicing; Named isoforms=3; Name=Alpha; IsoId=Q9UP52-1; Sequence=Displayed; Name=Beta; IsoId=Q9UP52-2; Sequence=VSP_005354; Name=Gamma; IsoId=Q9UP52-3; Sequence=VSP_005355.
[TISSUE SPECIFICITY] Predominantly expressed in liver. While the alpha form is also expressed in spleen, lung, muscle, prostate and peripheral blood mononuclear cells, the beta form is expressed in all tissues tested, albeit weakly.
[DISEASE] Defects in TFR2 are a cause of hereditary hemochromatosis type 3 (HFE3) [MIM:604250]. HFE3 is a disorder of iron hemostasis resulting in iron overload and has a phenotype indistinguishable from that of hereditary hemochromatosis (HH). HH is characterized by abnormal intestinal iron absorption and progressive increase of total body iron, which results in midlife in clinical complications including cirrhosis, cardiopathy, diabetes, endocrine dysfunctions, arthropathy, and susceptibility to liver cancer. Since the disease complications can be effectively prevented by regular phlebotomies, early diagnosis is most important to provide a normal life expectancy to the affected subjects.
[MISCELLANEOUS] The variant lys-172 found in hereditary hemochromatosis type III affects the putative initiation codon of the beta isoform thus preventing its translation.
[SIMILARITY] BELONGS TO PEPTIDASE FAMILY M28B.

```
FEATURES             Location/Qualifiers
     source          1..801
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
     gene            1..801
                     /gene="TFR2"
     Protein         1..801
                     /gene="TFR2"
                     /product="Transferrin receptor protein 2"
     Region          1..171
                     /gene="TFR2"
                     /region_name="Splicing variant"
                     /note="Missing (in isoform Beta). /FTId=VSP_005354."
     Region          1..83
                     /gene="TFR2"
                     /region_name="Domain"
                     /note="CYTOPLASMIC (POTENTIAL)."
     Site            23..26
                     /gene="TFR2"
                     /site_type="unclassified"
                     /note="ENDOCYTOSIS SIGNAL (POTENTIAL)."
     Region          84..104
                     /gene="TFR2"
                     /region_name="Transmembrane region"
                     /note="SIGNAL-ANCHOR (TYPE-II MEMBRANE PROTEIN)
                     (POTENTIAL)."
     Region          105..801
                     /gene="TFR2"
                     /region_name="Domain"
                     /note="EXTRACELLULAR (POTENTIAL)."
     Bond            bond(108)
                     /gene="TFR2"
                     /bond_type="disulfide"
                     /note="INTERCHAIN (POTENTIAL)."
     Bond            bond(111)
                     /gene="TFR2"
                     /bond_type="disulfide"
                     /note="INTERCHAIN (POTENTIAL)."
     Region          172
                     /gene="TFR2"
                     /region_name="Variant"
                     /note="M -> K (IN HFE3). /FTId=VAR_012738."
     Site            240
                     /gene="TFR2"
                     /site_type="glycosylation"
                     /note="N-LINKED (GLCNAC...) (POTENTIAL)."
     Site            339
                     /gene="TFR2"
                     /site_type="glycosylation"
                     /note="N-LINKED (GLCNAC...) (POTENTIAL)."
     Region          343..369
                     /gene="TFR2"
                     /region_name="Splicing variant"
                     /note="Missing (in isoform Gamma). /FTId=VSP_005355."
     Site            540
                     /gene="TFR2"
                     /site_type="glycosylation"
                     /note="N-LINKED (GLCNAC...) (POTENTIAL)."
     Region          712
                     /gene="TFR2"
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                     /region_name="Conflict"
                     /note="R -> RIPLSAQV (IN REF. 2)."
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                     /site_type="glycosylation"
                     /note="N-LINKED (GLCNAC...) (POTENTIAL)."
ORIGIN
        1 merlwglfqr aqqlsprssq tvyqrvegpr kghleeeeed geegaetlah fcpmelrgpe
       61 plgsrprqpn lipwaaagrr aapylvltal liftgafllg yvafrgscqa cgdsvlvvse
      121 dvnyepdldf hqgrlywsdl qamflqflge grledtirqt slrervagsa gmaaltqdir
      181 aalsrqkldh vwtdthyvgl qfpdpahpnt lhwvdeagkv geqlpledpd vycpysaign
      241 vtgelvyahy grpedlqdlr argvdpvgrl llvrvgvisf aqkvtnaqdf gaqgvliype
      301 padfsqdppk pslssqqavy ghvhlgtgdp ytpgfpsfnq tqfppvassg lpsipaqpis
      361 adiasrllrk lkgpvapqew qgsllgspyh lgpgprlrlv vnnhrtstpi nnifgciegr
      421 sepdhyvvig aqrdawgpga aksavgtail lelvrtfssm vsngfrprrs llfiswdggd
      481 fgsvgstewl egylsvlhlk avvyvsldna vlgddkfhak tsplltslie svlkqvdspn
      541 hsgqtlyeqv vftnpswdae virplpmdss aysftafvgv pavefsfmed dqaypflhtk
      601 edtyenlhkv lqgrlpavaq avaqlagqll irlshdrllp ldfgrygdvv lrhignlnef
      661 sgdlkarglt lqwvysargd yiraaeklrq eiysseerde rltrmynvri mrvefyflsq
      721 yvspadspfr hifmgrgdht lgalldhlrl lrsnssgtpg atsstgfqes rfrrqlallt
      781 wtlqgaanal sgdvwnidnn f
//
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NCBI Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.5 [Nov-16-2002]

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.000 wordsize: 3 Filter Align

Sequence 1 lcl|seq_1 **Length** 560 GPNMB X76534
Sequence 2 lcl|seq_2 **Length** 760 Transferrin Receptor 1 P02786

No significant similarity was found

NCBI Blast 2 Sequences results

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.5 [Nov-16-2002]

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.000 wordsize: 3 Filter ☐ Align

Sequence 1 lcl|seq_1 **Length** 560 GPNMB Y76534
Sequence 2 lcl|seq_2 **Length** 801 Transferrin Receptor Protein 2 Q9UP52
No significant similarity was found

1: NP_066563. neuromedin B [Hom...[gi:10835107] BLink, Links

```
LOCUS       NMB                     121 aa            linear   PRI 06-APR-2003
DEFINITION  neuromedin B [Homo sapiens].
ACCESSION   NP_066563
VERSION     NP_066563.1  GI:10835107
DBSOURCE    REFSEQ: accession NM_021077.2
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 121)
  AUTHORS   Richard,I., Broux,O., Chiannilkulchai,N., Fougerousse,F.,
            Allamand,V., Bourg,N., Brenguier,L., Devaud,C., Pasturaud,P.,
            Roudaut,C. et al.
  TITLE     Regional localization of human chromosome 15 loci
  JOURNAL   Genomics 23 (3), 619-627 (1994)
  MEDLINE   95154832
   PUBMED   7851890
REFERENCE   2  (residues 1 to 121)
  AUTHORS   Krane,I.M., Naylor,S.L., Helin-Davis,D., Chin,W.W. and Spindel,E.R.
  TITLE     Molecular cloning of cDNAs encoding the human bombesin-like peptide
            neuromedin B. Chromosomal localization and comparison to cDNAs
            encoding its amphibian homolog ranatensin
  JOURNAL   J. Biol. Chem. 263 (26), 13317-13323 (1988)
  MEDLINE   88330837
   PUBMED   2458345
COMMENT     PROVISIONAL REFSEQ: This record has not yet been subject to final
            NCBI review. The reference sequence was derived from M21551.1.
FEATURES             Location/Qualifiers
     source          1..121
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                     /db_xref="taxon:9606"
                     /chromosome="15"
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                     /tissue_type="hypothalamus"
                     /tissue_lib="of R.Goodman"
     Protein         1..121
                     /product="neuromedin B"
     sig_peptide     1..24
                     /gene="NMB"
                     /note="G00-120-237"
     mat_peptide     25..57
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                     /note="G00-120-237"
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                     /gene="NMB"
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                     /coded_by="NM_021077.2:37..402"
                     /db_xref="LocusID:4828"
                     /db_xref="MIM:162340"
ORIGIN
        1 marraggarm fgslllfall aagvaplswd lpeprsrask irvhsrgnlw atghfmgkks
       61 lepsspshwg qlptpplrdq rlqlshdllg illlkkalgv slsrpapqiq yrrllvqilq
      121 k
//
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1: NP_002501. glycoprotein (tra...[gi:4505405] BLink, Domains, Links

```
LOCUS       GPNMB                     560 aa            linear   PRI 05-APR-2003
DEFINITION  glycoprotein (transmembrane) nmb; transmembrane glycoprotein [Homo
            sapiens].
ACCESSION   NP_002501
VERSION     NP_002501.1  GI:4505405
DBSOURCE    REFSEQ: accession NM_002510.1
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 560)
  AUTHORS   Weterman,M.A., Ajubi,N., van Dinter,I.M., Degen,W.G., van
            Muijen,G.N., Ruitter,D.J. and Bloemers,H.P.
  TITLE     nmb, a novel gene, is expressed in low-metastatic human melanoma
            cell lines and xenografts
  JOURNAL   Int. J. Cancer 60 (1), 73-81 (1995)
  MEDLINE   95113576
   PUBMED   7814155
COMMENT     REVIEWED REFSEQ: This record has been curated by NCBI staff. The
            reference sequence was derived from X76534.1.

            Summary: GPNMB is a transmembrane glycoprotein which shows homology
            to the pMEL17 precursor, a melanocyte-specific protein. GPNMB shows
            expression in the lowly metastatic human melanoma cell lines and
            xenografts but does not show expression in the highly metastatic
            cell lines; although, it is also expressed in other tissues and
            tumor cell lines as well. GPNMB may be involved in growth delay and
            reduction of metastatic potential.
FEATURES             Location/Qualifiers
     source          1..560
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="7"
                     /map="7p15"
     Protein         1..560
                     /product="glycoprotein (transmembrane) nmb"
                     /note="transmembrane glycoprotein"
     variation       195
                     /allele="C"
                     /allele="S"
                     /db_xref="dbSNP:530436"
     variation       197
                     /allele="H"
                     /allele="N"
                     /db_xref="dbSNP:530413"
     Region          259..319
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                     (PKD1) and other proteins"
                     /note="PKD"
                     /db_xref="CDD:smart00089"
     CDS             1..560
                     /gene="GPNMB"
                     /coded_by="NM_002510.1:92..1774"
                     /db_xref="LocusID:10457"
                     /db_xref="MIM:604368"
ORIGIN
        1 meclyyflgf lllaarlpld aakrfhdvlg nerpsaymre hnqlngwssd endwneklyp
       61 vwkrgdmrwk nswkggrvqa vltsdspalv gsnitfavnl ifprcqkeda ngnivyeknc
      121 rneaglsadp yvynwtawse dsdgengtgq shhnvfpdgk pfphhpgwrr wnfiyvfhtl
      181 gqyfqklgrc svrvsvntan vtlgpqlmev tvyrrhgray vpiaqvkdvy vvtdqipvfv
      241 tmfqkndrns sdetflkdlp imfdvlihdp shflnystin ykwsfgdntg lfvstnhtvn
      301 htyvlngtfs lnltvkaaap gpcppppppp rpskptpslg pagdnplels ripdencqin
      361 ryghfqatit ivegilevni iqmtdvlmpv pwpesslidf vvtcqgsipt evctiisdpt
      421 ceitqntvcs pvdvdemcll tvrrtfngsg tycvnltlgd dtslaltstl isvpdrdpas
      481 plrmansali svgclaifvt visllvykkh keynpiensp gnvvrskgls vflnrakavf
      541 fpgnqekdpl lknqefkgvs
//
```

NCBI Blast 2 Sequences results

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.5 [Nov-16-2002]

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.000 wordsize: 3 Filter Align

Sequence 1 lcl|seq_1 **Length** 121 NMB NP_066563

Sequence 2 lcl|seq_2 **Length** 560 GPNMB NP_002501

No significant similarity was found

NCBI

results of BLAST

BLASTP 2.2.6 [Apr-09-2003]

Reference:
Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.

RID: 1051035808-05395-3586

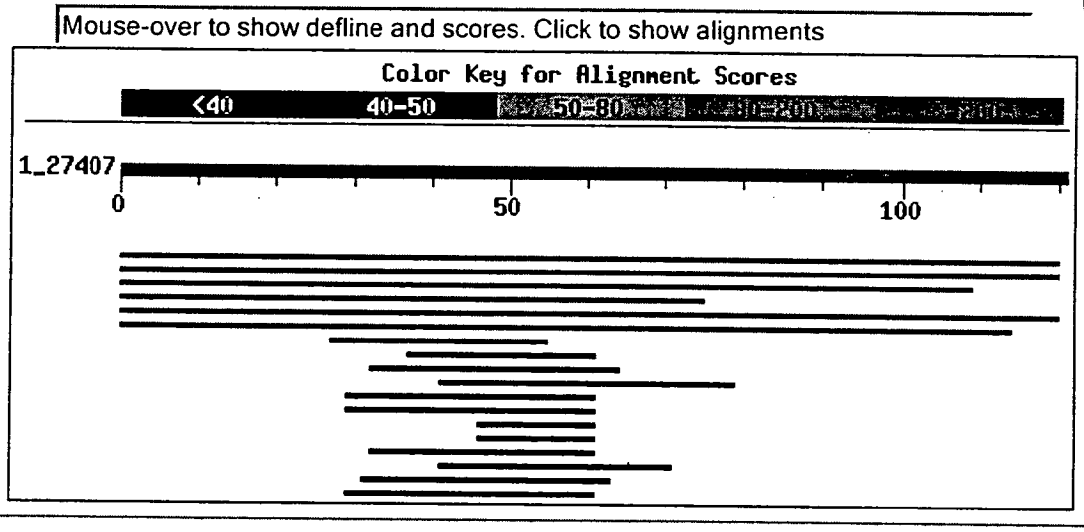
Query=
(121 letters)

Database: All non-redundant GenBank CDS translations+PDB+SwissProt+PIR+PRF
1,415,660 sequences; 455,667,871 total letters

If you have any problems or questions with the results of this search please refer to the **BLAST FAQs**

Taxonomy reports

Distribution of 18 Blast Hits on the Query Sequence



Sequences producing significant alignments:	Score (bits)	E Value	
gi|10835107|ref|NP_066563.1| neuromedin B [Homo sapiens] >g...	149	9e-36	L
gi|20141490|sp|P08949|NEUB_HUMAN Neuromedin B-32 precursor ...	131	2e-30	L
gi|13938517|gb|AAH07407.1|AAH07407 Similar to neuromedin B ...	118	2e-26	
gi|88253|pir||A28945 neuromedin B precursor - human	103	4e-22	

gi|13386018|ref|NP_080799.1| RIKEN cDNA 3110023K12 [Mus mus...	93	9e-19
gi|112182|pir||A37178 neuromedin B precursor - rat	91	5e-18
gi|128094|sp|P01297|NEUB_PIG Neuromedin B-32 [Contains: Neu...	52	1e-06
gi|121641|sp|P29007|GRP_BOMOR Gastrin-releasing peptide pre...	35	0.18
gi|1237140|gb|AAC59785.1| SAP bombesin preprohormone	34	0.36
gi|9049482|gb|AAF82387.1|AF111028_1 gastrin-releasing pepti...	34	0.52
gi|422599|pir||A47201 bombesinlike peptide - African clawed...	33	0.63
gi|1171692|sp|P43443|NEUB_XENLA Neuromedin B precursor >gi|...	33	0.69
gi|1237138|gb|AAC59784.1| Phe-13 bombesin preprohormone >gi...	33	0.72
gi|115097|sp|P01296|BOMB_BOMVA Bombesin precursor >gi|25763...	32	2.3
gi|115096|sp|P21591|BOMB_BOMOR Bombesin precursor >gi|10397...	31	2.8
gi|87496|pir||A26182 gastrin-releasing peptide precursor sp...	30	5.0
gi|1346185|sp|P47851|GRP_SHEEP Gastrin-releasing peptide pr...	30	7.8
gi|2506229|sp|P08947|LITP_PHYSA [Phe8]-phyllolitorin precur...	30	8.6

Alignments

Get selected sequences | Select all | Deselect all

>gi|10835107|ref|NP_066563.1| neuromedin B [Homo sapiens]
gi|189228|gb|AAA59934.1| neuromedin B
Length = 121

Score = 149 bits (376), Expect = 9e-36
Identities = 90/121 (74%), Positives = 90/121 (74%)

```
Query: 1   MARRAGGARMFGSXXXXXXXXXXXXXXXSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60
            MARRAGGARMFGS               SWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS
Sbjct: 1   MARRAGGARMFGSLLLFALLAAGVAPLSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60

Query: 61  LEPSSPSHWGQLPTPPLRDQRXXXXXXXXXXXXXXXXGVSLSRPAPQIQYRRLLVQILQ 120
            LEPSSPSHWGQLPTPPLRDQR                GVSLSRPAPQIQYRRLLVQILQ
Sbjct: 61  LEPSSPSHWGQLPTPPLRDQRLQLSHDLLGILLLKKALGVSLSRPAPQIQYRRLLVQILQ 120

Query: 121 K 121
            K
Sbjct: 121 K 121
```

>gi|20141490|sp|P08949|NEUB_HUMAN Neuromedin B-32 precursor [Contains: Neuromedi
gi|14250345|gb|AAH08603.1|AAH08603 neuromedin B [Homo sapiens]
Length = 121

Score = 131 bits (329), Expect = 2e-30
Identities = 82/121 (67%), Positives = 82/121 (67%)

```
Query: 1   MARRAGGARMFGSXXXXXXXXXXXXXXXSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60
            MARRAGGARMFGS               SWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS
Sbjct: 1   MARRAGGARMFGSLLLFALLAAGVAPLSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60

Query: 61  LEPSSPSHWGQLPTPPLRDQRXXXXXXXXXXXXXXXXGVSLSRPAPQIQYRRLLVQILQ 120
            LEPSSPS G     LRDQR                GVSLSRPAPQIQYRRLLVQILQ
Sbjct: 61  LEPSSPSPLGTATHTSLRDQRLQLSHDLLGILLLKKALGVSLSRPAPQIQYRRLLVQILQ 120
```

```
Query: 121 K 121
           K
Sbjct: 121 K 121
```

>gi|13938517|gb|AAH07407.1|AAH07407 Similar to neuromedin B [Homo sapiens]
gi|13938561|gb|AAH07431.1|AAH07431 Similar to neuromedin B [Homo sapiens]
Length = 154

Score = 118 bits (295), Expect = 2e-26
Identities = 71/110 (64%), Positives = 71/110 (64%)

```
Query: 1   MARRAGGARMFGSXXXXXXXXXXXXXXXSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60
            MARRAGGARMFGS               SWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS
Sbjct: 1   MARRAGGARMFGSLLLFALLAAGVAPLSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60

Query: 61  LEPSSPSHWGQLPTPPLRDQRXXXXXXXXXXXXXXXXXGVSLSRPAPQIQ 110
            LEPSSPS  G      LRDQR                  GVSLSRPAPQIQ
Sbjct: 61  LEPSSPSPLGTATHTSLRDQRLQLSHDLLGILLLKKALGVSLSRPAPQIQ 110
```

>gi|88253|pir||A28945 neuromedin B precursor - human
Length = 76

Score = 103 bits (258), Expect = 4e-22
Identities = 62/76 (81%), Positives = 62/76 (81%)

```
Query: 1  MARRAGGARMFGSXXXXXXXXXXXXXXXSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60
           MARRAGGARMFGS               SWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS
Sbjct: 1  MARRAGGARMFGSLLLFALLAAGVAPLSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60

Query: 61 LEPSSPSHWGQLPTPP 76
           LEPSSPSHWGQLPTPP
Sbjct: 61 LEPSSPSHWGQLPTPP 76
```

>gi|13386018|ref|NP_080799.1| RIKEN cDNA 3110023K12 [Mus musculus]
gi|20139148|sp|Q9CR53|NEUB_MOUSE Neuromedin B-32 precursor [Contains: Neuromedin
gi|12848356|dbj|BAB27922.1| unnamed protein product [Mus musculus]
gi|12851724|dbj|BAB29144.1| unnamed protein product [Mus musculus]
gi|20306611|gb|AAH28490.1| RIKEN cDNA 3110023K12 [Mus musculus]
Length = 121

Score = 92.8 bits (229), Expect = 9e-19
Identities = 61/121 (50%), Positives = 68/121 (56%)

```
Query: 1   MARRAGGARMFGSXXXXXXXXXXXXXXXSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60
            M R+AG + +                  +WDLPEPRSRASKIRVH RGNLWATGHFMGKKS
Sbjct: 1   MTRQAGSSWLLRGLLLFALFASGVAPFNWDLPEPRSRASKIRVHPRGNLWATGHFMGKKS 60

Query: 61  LEPSSPSHWGQLPTPPLRDQRXXXXXXXXXXXXXXXXXGVSLSRPAPQIQYRRLLVQILQ 120
            LEP S S  G  P    RDQR                  G++ S PAP IQYRRLL  +LQ
Sbjct: 61  LEPPSLSLVGTAPPNTPRDQRLQLSHDLLRILLRKKALGMNFSGPAPPIQYRRLLEPLLQ 120

Query: 121 K 121
```

```
            K
Sbjct: 121 K 121
```

>gi|112182|pir||A37178 neuromedin B precursor - rat
Length = 117

Score = 90.5 bits (223), Expect = 5e-18
Identities = 59/115 (51%), Positives = 64/115 (55%)

```
Query: 1   MARRAGGARMFGSXXXXXXXXXXXXXXXSWDLPEPRSRASKIRVHSRGNLWATGHFMGKKS 60
            M R+AG   +                  SWDLPEPRSRASKIRVH RGNLWATGHFMGKKS
Sbjct: 1   MTRQAGSTWLLRGLLLFALFVSGITPFSWDLPEPRSRASKIRVHPRGNLWATGHFMGKKS 60

Query: 61  LEPSSPSHWGQLPTPPLRDQRXXXXXXXXXXXXXXXXXGVSLSRPAPQIQYRRLL 115
            LEP S S  G  P    R+QR                G++LS PAP IQYRRLL
Sbjct: 61  LEPPSLSLVGTAPPITQREQRLQLSHDLLRILLLQKALGMNLSGPAPPIQYRRLL 115
```

>gi|128094|sp|P01297|NEUB_PIG Neuromedin B-32 [Contains: Neuromedin B]
gi|69282|pir||BSPGNB neuromedin B-32 - pig
Length = 32

Score = 52.4 bits (124), Expect = 1e-06
Identities = 27/29 (93%), Positives = 27/29 (93%)

```
Query: 28 SWDLPEPRSRASKIRVHSRGNLWATGHFM 56
          SWDLPEPRSRA KIRVH RGNLWATGHFM
Sbjct: 4  SWDLPEPRSRAGKIRVHPRGNLWATGHFM 32
```

>gi|121641|sp|P29007|GRP_BOMOR Gastrin-releasing peptide precursor (GRP-29) [Cor
Neuromedin C (GRP-10); C-terminal extension peptide
(CTEP)]
gi|283791|pir||A42437 gastrin-releasing peptide - Bombina orientalis
gi|211019|gb|AAA51409.1| gastrin-releasing peptide
Length = 155

Score = 35.4 bits (80), Expect = 0.18
Identities = 14/25 (56%), Positives = 19/25 (76%)

```
Query: 38 ASKIRVHSRGNLWATGHFMGKKSLE 62
          AS  +++ RG+ WA GH MGKKS+E
Sbjct: 42 ASLSKIYPRGSHWAVGHLMGKKSIE 66
```

>gi|1237140|gb|AAC59785.1| SAP bombesin preprohormone
Length = 119

Score = 34.3 bits (77), Expect = 0.36
Identities = 15/33 (45%), Positives = 21/33 (63%)

```
Query: 33 EPRSRASKIRVHSRGNLWATGHFMGKKSLEPSS 65
          +P ++       S GN WA GHFMGKKSL+ ++
Sbjct: 35 DPNNQGGLSLQQSLGNQWARGHFMGKKSLQDTN 67
```

>gi|9049482|gb|AAF82387.1|AF111028_1 gastrin-releasing peptide precursor [Carass
Length = 157

Score = 33.9 bits (76), Expect = 0.52
Identities = 19/43 (44%), Positives = 23/43 (53%), Gaps = 5/43 (11%)

```
Query: 42 RVHSRGNLWATGHFMGKKS----LEPSSPSHWGQLPTPPLRDQ 80
          +V+ RGN WA GH MGKKS    + P  P    G   +   RDQ
Sbjct: 35 KVYPRGNHWAVGHLMGKKSTDEQVRPEDPED-GDETSMTTRDQ 76
```

>gi|422599|pir||A47201 bombesinlike peptide - African clawed frog
Length = 120

Score = 33.5 bits (75), Expect = 0.63
Identities = 18/33 (54%), Positives = 20/33 (60%), Gaps = 3/33 (9%)

```
Query: 30 DLPEPRSRASKIRVHSRGNLWATGHFMGKKSLE 62
          +  E      KIR   RGN WA GHFMGKKSL+
Sbjct: 31 EFSEDARNIEKIR---RGNQWAIGHFMGKKSLQ 60
```

>gi|1171692|sp|P43443|NEUB_XENLA Neuromedin B precursor
gi|214614|gb|AAA49912.1| neuromedin
Length = 120

Score = 33.5 bits (75), Expect = 0.69
Identities = 18/33 (54%), Positives = 20/33 (60%), Gaps = 3/33 (9%)

```
Query: 30 DLPEPRSRASKIRVHSRGNLWATGHFMGKKSLE 62
          +  E      KIR   RGN WA GHFMGKKSL+
Sbjct: 31 EFSEDARNIEKIR---RGNQWAIGHFMGKKSLQ 60
```

>gi|1237138|gb|AAC59784.1| Phe-13 bombesin preprohormone
gi|1589538|prf||2211320A bombesin
Length = 119

Score = 33.5 bits (75), Expect = 0.72
Identities = 13/16 (81%), Positives = 14/16 (87%)

```
Query: 47 GNLWATGHFMGKKSLE 62
          GN WA GHFMGKKSL+
Sbjct: 49 GNQWAVGHFMGKKSLQ 64
```

>gi|115097|sp|P01296|BOMB_BOMVA Bombesin precursor
gi|25763397|pir||BSTDY bombesin precursor - yellow-bellied toad
gi|65309|emb|CAA36686.1| bombesin [Bombina variegata]
Length = 107

Score = 31.6 bits (70), Expect = 2.3
Identities = 12/16 (75%), Positives = 13/16 (81%)

```
Query: 47 GNLWATGHFMGKKSLE 62
          GN WA GH MGKKSL+
Sbjct: 46 GNQWAVGHLMGKKSLQ 61
```

>gi|115096|sp|P21591|BOMB_BOMOR Bombesin precursor
gi|103971|pir||A39261 bombesin precursor - Bombina orientalis
gi|211017|gb|AAA48551.1| bombesin
Length = 119

Score = 31.2 bits (69), Expect = 2.8
Identities = 15/31 (48%), Positives = 19/31 (61%), Gaps = 1/31 (3%)

```
Query: 33 EPRSRASKIRVHSR-GNLWATGHFMGKKSLE 62
          E  +   +I +  R GN WA GH MGKKSL+
Sbjct: 34 EDPNNQGRISLQQRLGNQWAVGHLMGKKSLQ 64
```

>gi|87496|pir||A26182 gastrin-releasing peptide precursor splice form III - huma
Length = 138

Score = 30.4 bits (67), Expect = 5.0
Identities = 18/32 (56%), Positives = 21/32 (65%), Gaps = 1/32 (3%)

```
Query: 42 RVHSRGNLWATGHFMGKKSL-EPSSPSHWGQL 72
          +++ RGN WA GH MGKKS  E SS S  G L
Sbjct: 36 KMYPRGNHWAVGHLMGKKSTGESSSVSERGSL 67
```

>gi|1346185|sp|P47851|GRP_SHEEP Gastrin-releasing peptide precursor (GRP) [Conta
(GRP-10)]
gi|2136897|pir||I47010 gastrin-releasing peptide - sheep
gi|913168|gb|AAB32675.1| Gastrin-releasing peptide GRP [Ovis aries]
Length = 134

Score = 30.0 bits (66), Expect = 7.8
Identities = 17/42 (40%), Positives = 24/42 (57%), Gaps = 9/42 (21%)

```
Query: 32 PEPRSRASKI---------RVHSRGNLWATGHFMGKKSLEPS 64
          P PR  A+ +          ++++RGN WA GH MGKKS+  S
Sbjct: 17 PAPRGSAAPVTAGRAGALAKMYTRGNHWAVGHLMGKKSVAES 58
```

>gi|2506229|sp|P08947|LITP_PHYSA [Phe8]-phyllolitorin precursor
gi|1362698|pir||B57058 Phe-8 phyllolitorin precursor - Sauvage's leaf frog
gi|998450|gb|AAB32788.1| Phe8 phyllolitorin [Phyllomedusa sauvagei]
Length = 90

Score = 29.6 bits (65), Expect = 8.6
Identities = 17/33 (51%), Positives = 19/33 (57%), Gaps = 1/33 (3%)

```
Query: 30 DLPEPRSRASKIRVHSRGNLWATGHFMGKKSLE 62
```

```
          ++ E     SK  V  R  LWA G FMGKKSLE
Sbjct: 32 EVTEESDDLSKRNVLQR-QLWAVGSFMGKKSLE 63
```

Get selected sequences | Select all | Deselect all

```
  Database: All non-redundant GenBank CDS
  translations+PDB+SwissProt+PIR+PRF
    Posted date:  Apr 21, 2003  1:41 AM
  Number of letters in database: 455,667,871
  Number of sequences in database:  1,415,660

Lambda     K      H
   0.319    0.134    0.424

Gapped
Lambda     K      H
   0.267   0.0410    0.140


Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Hits to DB: 89,060,364
Number of Sequences: 1415660
Number of extensions: 2728065
Number of successful extensions: 4328
Number of sequences better than 10.0: 24
Number of HSP's better than 10.0 without gapping: 23
Number of HSP's successfully gapped in prelim test: 1
Number of HSP's that attempted gapping in prelim test: 4305
Number of HSP's gapped (non-prelim): 24
length of query: 121
length of database: 455,667,871
effective HSP length: 97
effective length of query: 24
effective length of database: 318,348,851
effective search space: 7640372424
effective search space used: 7640372424
T: 11
A: 40
X1: 16 ( 7.4 bits)
X2: 38 (14.6 bits)
X3: 64 (24.7 bits)
S1: 41 (21.8 bits)
S2: 65 (29.6 bits)
```